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EXAMINER	
NGUYEN, QUANG	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/827,854	ZANNIS ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2007 and 14 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79 and 83-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79 and 83-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *attached sequence search*.

DETAILED ACTION

Applicant's amendments filed on 12/14/06 and 3/14/07 were entered.

Amended claims 79 and 83-101 are pending in the present application, and they are examined on the merits herein with SEQ ID NO: 15 (apoE3) and adenoviral vector as the previously elected species. It is noted that SEQ ID NO: 2 is the mature apoE3 amino acid sequence, while SEQ ID NO: 15 is the apoE3 preproprotein containing its N-terminal signal peptide.

Response to Amendment

The provisional rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37, 39-40 and 42-58 of copending Application No. 11/220,485 was withdrawn because these claims were withdrawn in the co-pending Application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 79, 83-84, 86, 88 and 91-97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a modified rejection necessitated by Applicant's amendment.**

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method of lowering cholesterol in a mammal in need thereof without inducing hypertriglyceridemia, wherein said mammal expressing a functional low density lipoprotein (LDL) receptor, said method comprising intravascularly administering to said mammal a replication-defective adenoviral vector comprising a nucleic acid encoding any secreted polypeptide, wherein said polypeptide comprises an amino acid sequence having at least amino acids 1-185 of SEQ ID NO:2 or having at least 90% sequence identity to an amino acid sequence comprising at least amino acids 1-185 of SEQ ID NO:2, and as long as said nucleic acid does not encode amino acids 260-299 of SEQ ID NO:2. Once again, please note that the claims still encompass the utilization of an encoded polypeptide containing a carboxyl-terminal region of a mature, native, human apoE as long as the encoded polypeptide does not contain the sequence having amino acids 260-299 of SEQ ID NO: 2; and that the polypeptide comprises an amino acid sequence having at least amino acids 1-185 of SEQ ID NO:2 or having at

least 90% sequence identity to an amino acid sequence comprising at least amino acids 1-185 of SEQ ID NO:2.

Apart from the disclosure of amino acid sequences of various human apoE isoforms such as apoE4, apoE3, apoE2, apoE1, apoE2* and apoE2** with SEQ ID NOS: 14-19, respectively, and that the amino-terminal 1-185 residues of human apoE4 are sufficient for binding to lipoprotein remnants to an extent that promotes their efficient clearance in apoE-deficient mice, whereas the carboxyl-terminal 260-299 region of the human apoE4 contributes to hypertriglyceridemia, the specification fails to describe the essential characteristics or elements possessed by a representative number of species for a broad genus of the nucleic acid to be utilized in the method as claimed to lower the total serum cholesterol level without inducing hypertriglyceridemia. For example, the instant specification fails to describe which amino acids to be substituted, deleted or inserted, at which positions and in which combinations, particularly at a carboxyl-terminal region of a mature, native, human apoE or at regions other than the known allelic variant sites for the various apoE isoforms and the exemplified truncated region between amino acids 186-259 of SEQ ID NO:2, such that an encoded polypeptide having at least 90% sequence identity to an amino acid sequence comprising at least amino acid residues 1-185 of SEQ ID NO: 2 but without the amino acid sequence of amino acids 260-299 of SEQ ID NO: 2, still possesses the desired property, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia.

At the effective filing date (4/6/2000) of the present application, there were few findings indicated that under certain experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a mature, full-length human ApoE resulted in a reduction in the plasma total cholesterol level without an induction of hypertriglyceridemia (Tsukamoto et al., J. Clin. Invest. 100:107-114, 1997; Kashyap et al., J. Clin. Invest. 96:1612-1620, 1995). **More importantly, even one year after the effective filing date of the present application, Applicants still state "The identification of amino acid residues within the carboxyl terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE, is the subject of ongoing research"** (Kypreos et al., J. Biol. Chem. 276:19778-19786, 2001; page 19785, col. 2, bottom of the first full paragraph). Furthermore, variable isoform-specific effects of apoE polypeptides *in vivo* have also been reported (Yoshida et al., Circulation 104:2820-2825, 2001).

Thus, the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a representative number of species for a broad genus of a nucleic acid encoding any

secreted polypeptide, wherein said polypeptide comprises an amino acid sequence having at least amino acids 1-185 of SEQ ID NO:2 or having at least 90% sequence identity to an amino acid sequence comprising at least amino acids 1-185 of SEQ ID NO:2, and as long as said nucleic acid does not encode amino acids 260-299 of SEQ ID NO:2, to be utilized in the method as claimed to lower the total serum cholesterol level without inducing hypertriglyceridemia, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 79, 83-84, 86, 88, 91-97 and 101 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor, said method comprises intravascularly administering to said mammal a replication defective adenoviral vector encoding a secreted polypeptide consists of residues 1-185, 1-202, 1-203, 1-220, 1-229, 1-247 or 1-259 of any one of SEQ ID Nos. 14-19, or a population of a secreted truncated polypeptide

consisting of residues 1-259 of any one of SEQ ID Nos. 14-19 with one or more deletions of amino acids within 186-259 amino acid residues, with SEQ ID NO: 15 as the elected species, when expressed and secreted in said mammal, lowers the total serum cholesterol without inducing hypertriglyceridemia,

does not reasonably provide enablement for a method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor without inducing hypertriglyceridemia by intravascularly administering to said mammal other recombinant replication-defective adenoviral vector as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. ***This is a modified rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing the construction of recombinant adenoviruses expressing secreted apoE4 and various secreted truncated forms of apoE4 (e.g., apoE4-185, apoE4-202, apoE4-229, EpoE4-259). In an apoE-deficient mouse model, the recombinant adenoviruses were injected intravenously through the tail vein and the effects of full-length apoE4 and its various truncated forms

on cholesterol and triglyceride homeostasis were evaluated. Applicants showed that an insignificant reduction of the mouse cholesterol level and a severely induced hypertriglyceridemia were observed in apoE-deficient mice treated with full-length apoE4-adenovirus, whereas reduced levels of cholesterol without the induction of hypertriglyceridemia were obtained in animals treated with recombinant adenoviruses expressing the aforementioned truncated forms of apoE4. Applicants further demonstrated that overexpression of either full-length apoE3 or apoE4 is sufficient to induce combined hyperlipedimia (high cholesterol and triglyceride levels) in normal C57BL6 mice, whereas an overexpression of apoE4-202 has no detectable effect on triglyceride levels of the C57BL6 mice.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(a) The breadth of the claims

The broad claims encompass a method of lowering cholesterol in a mammal in need thereof without inducing hypertriglyceridemia, wherein said mammal expressing a functional low density lipoprotein (LDL) receptor, said method comprising intravascularly administering to said mammal a replication-defective adenoviral vector comprising a nucleic acid encoding any secreted polypeptide, wherein said polypeptide comprises an amino acid sequence having at least amino acids 1-185 of SEQ ID NO:2 or having at least 90% sequence identity to an amino acid sequence comprising at least amino acids 1-185 of SEQ ID NO:2, and as long as said nucleic acid does not encode amino acids

260-299 of SEQ ID NO:2. As written, the claims still encompass the utilization of an encoded polypeptide containing a carboxyl-terminal region of a mature, native, human apoE as long as the encoded polypeptide does not contain the sequence having amino acids 260-299 of SEQ ID NO: 2; and that the polypeptide comprises an amino acid sequence having at least amino acids 1-185 of SEQ ID NO:2 or having at least 90% sequence identity to an amino acid sequence comprising at least amino acids 1-185 of SEQ ID NO:2. Claim 101 recites specifically the same method, wherein the nucleic acid encodes amino acids 1-277 of an apoE preprotein of any one of SEQ ID Nos. 14-19.

(b) The state and the unpredictability of the art

The nature of the instant claims falls within the realm of gene therapy. At the effective filing date of the present application (4/6/2000), the state of the gene therapy art was and still remains unpredictable with respect to the attainment of desired therapeutic effects, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor, as evidenced by the reviews of Verma et al. (Nature 389:239-242, 1997; IDS), Dang et al. (Clin. Cancer Res. 5:471-474, 1999), Romano et al. (Stem Cells 18:19-39, 2000) and Kawashiri et al. (Curr. Control Trials Cardiovasc. Med. 1:120-127, 2000). Dang et al. stated "Although significant progress has been achieved in our understanding of the limitations of gene therapy by suboptimal vectors, host immunological responses to the vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues" (page 474, col. 2, last paragraph). Romano et al. stated "The potential therapeutic

applications of gene transfer technology are enormous. However, the effectiveness of gene therapy programs is still questioned" (see abstract), and "Despite the latest progress reported in the area of vector design, research strategies still have to tackle critically important issues, such as further improvement of gene transfer technology, especially for *in vivo* gene delivery applications, regulation and control of the transgene expression post-cell transduction, and a variety of complex safety matters. These three main issues are to some extent intertwined and pose severe limitations on the applications of gene transfer technology in therapy" (page 21, col. 1, first paragraph). In October 2000, Kawashiri et al. still stated "Somatic gene therapy is a viable approach to the therapy of several lipid disorders for which therapies are currently inadequate" and "The next decade is therefore likely to witness several clinical trials of gene therapy for lipid disorders" (see Conclusion section, page 125). Kypreos et al. (FASEB J. 15:1598-1600, 2001) also stated "One major parameter in successful gene therapy approaches is **gene dosage** and **expression levels**....The inability of the truncated apoE forms that lack all or part of the carboxyl-terminal 260-299 region to induce hypertriglyceridemia, coupled with their intact ability to clear cholesterol, makes them attractive candidates in future gene therapy applications to correct remnant removal disorders" (page 1600, col. 2, last paragraph). Thus, it is clear that at the effective filing date of the present application gene therapy for the treatment of any lipid disorder was still immature and not routine.

Additionally, at the effective filing date of the present application (4/6/2000) although substantial evidence in the prior art as well as the findings of the present

invention suggested or indicated that ApoE functioned **to decrease cholesterol while increasing triglyceride levels** (see references cited on page 6, lines 4-25 of the instant specification), the findings of Tsukamoto et al. (J. Clin. Invest. 100:107-114, 1997; Cited previously) and Kashyap et al. (J. Clin. Invest. 96:1612-1620, 1995) indicated that under their experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a mature, full-length human ApoE (299 amino acid residues) resulted in **a reduction in the plasma total cholesterol level without an induction of hypertriglyceridemia**. Thus, at the effective filing date of the present application it was apparent that the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo*, at least in ApoE-deficient mice, was still unpredictable, let alone in any mammal expressing a functional LDL receptor.

The unpredictability of the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo* is further supported by the results of Yoshida et al. (Circulation 104:2820-2825, 2001) that showed that ApoE-deficient mice receiving apoE-/- bone marrow cells that express human apoE3 or apoE2 or apoEcys142 have cholesterol levels increasing with age and the cholesterol levels are not affected by apoE expression (see abstract). Interestingly, the lesion in male apoE3 mice was 40% smaller than that of control mice, while the lesion of apoE2 mice was similar to that of control mice and apoEcys142 mice showed an unexpected and significant increase in lesion size. It is further noted that ApoE2 differs from apoE3 by having a cysteine instead of an arginine at residue 158; and apoEcys142 contains 2

amino acid substitutions: an arginine substitution for cysteine at residue 142 and an arginine for cysteine substitution at residue 112.

(c) The amount of direction or guidance presented

Apart from the exemplification using an apoE-deficient mouse model with recombinant adenoviruses expressing secreted apoE4 or one of the secreted truncated apoE variants apoE4-185, apoE4-202, apoE4-229, EpoE4-259, the instant specification fails to provide sufficient guidance for a skilled artisan on how to lower the total serum cholesterol level without inducing hypertriglyceridemia in a mammal using a replication-defective adenoviral vector comprising a nucleic acid encoding a secreted polypeptide as broadly claimed. The instant specification fails to provide sufficient guidance for a skilled artisan on which modification(s), for example deletion, insertion or substitution, in which combination(s), and at which amino acid residues in the encoded secreted polypeptide, particularly in the carboxyl-terminal region of a mature, native, human apoE, or at regions other than the known allelic variant sites for the various apoE isoforms and the exemplified truncated region between amino acids 186-259 of SEQ ID NO:2, as long as said polypeptide having at least 90% sequence identity to an amino acid sequence comprising at least amino acid residues 1-185 of SEQ ID NO: 2 but without the amino acid sequence of amino acids 260-299 of SEQ ID NO: 2, still possesses the desired property, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor. Additionally, at the effective filing date of the present application, there was no evidence of record in the present application or in the prior art indicating that an

encoded apoE3-277 possesses the ability to lower the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor. As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. Guo et al. (PNAS 101:9205-9210, 2004) estimated that only about a third of single amino acid changes would completely inactivate the average protein and increasing the number of substitutions additively increases the probability that the protein would be inactivated and that specific proteins may be more or less tolerant to changes (see the entire article). Moreover, even one year after the effective filing date of the present application, Applicants still state "**The identification of amino acid residues within the carboxyl terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE, is the subject of ongoing research**" (Kypreos et al., J. Biol. Chem. 276:19778-19786, 2001; page 19785, col. 2, bottom of the first full paragraph). Furthermore, Yoshida et al. (Circulation 104:2820-2825, 2001) demonstrated that a single amino acid substitution between ApoE2 and ApoE3 proteins can have a significant effect in their biological acitivity *in vivo*, let alone for the breadth of the encoded secreted polypeptide to be utilized in the method as claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the gene therapy as well as the relevant art on the biological activity of apoE protein in lowering the total serum cholesterol level without inducing hypertriglyceridemia, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Amendment

Applicant's arguments related to the above rejections (lack of Written Description and Enablement) in the Amendment filed on 3/14/07 (pages 8-9) have been fully considered, but they are respectfully not found persuasive.

Applicants argue basically that the instant amended claims recite nucleic acid molecules that encode apoE polypeptides having at least amino acids 1-185 of SEQ ID NO:2 and one or more additionally residues between 186-259 of SEQ ID NO:2. These encoded polypeptides lack amino acids 260-299 of SEQ ID NO:2, the residues of apoE which were identified by Applicants as responsible for causing hypertriglyceridemia in mammals. Based on Applicant's description of the apoE polypeptides and in light of the amended claims, Applicants have satisfied the written description requirement under 35 USC 112, first paragraph. Applicants further argue that given the breadth of Applicants' disclosure, the amount of guidance provided in the specification, the presence of working examples, the level of skill in the art, the identification of desirable apoE

polypeptides requires no more than routine methods and does not constitute undue experimentation; and therefore the scope of presently amended claims are enabled.

Firstly, please note that as written, the amended claims simply do not simply encompass only nucleic acid molecules that encode apoE polypeptides having at least amino acids 1-185 of SEQ ID NO:2 and one or more additionally residues between 186-259 of SEQ ID NO:2 (please also note claim 101). The amended claims still encompass the utilization of an encoded polypeptide containing a carboxyl-terminal region of a mature, native, human apoE as long as the encoded polypeptide does not contain the sequence having amino acids 260-299 of SEQ ID NO: 2; and that the polypeptide comprises an amino acid sequence having at least amino acids 1-185 of SEQ ID NO:2 or having at least 90% sequence identity to an amino acid sequence comprising at least amino acids 1-185 of SEQ ID NO:2. Refer to the above modified rejections why the specification is still rejected for the lack of Written Description and Enablement apart from the revised scope of enablement after taking into account of Applicant's intention of claiming nucleic acid molecules that encode apoE polypeptides having at least amino acids 1-185 of SEQ ID NO:2 and one or more additionally residues between 186-259 of SEQ ID NO:2.

Secondly, apart from the enabled scope given it would have required undue experimentation to make and/or use the instant broadly claimed invention due to the unpredictability for obtaining the desired effects, lowering cholesterol without inducing hypertriglyceridemia in a mammal, in light of the overall teachings of (Tsukamoto et al., J. Clin. Invest. 100:107-114, 1997; Kashyap et al., J. Clin. Invest. 96:1612-1620, 1995);

Yoshida et al. (Circulation 104:2820-2825, 2001); Kypreos et al., J. Biol. Chem. 276:19778-19786, 2001); and Guo et al. (PNAS 101:9205-9210, 2004) as set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 79, 83-86, 90-91 and 93-99 are rejected under 35 U.S.C. 102(b) as being anticipated by McClelland et al (WO 96/14837) as evidenced by Wetterau et al (J. Biol. Chem. 263:6240-6248, 1988) and Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited previously). ***This is a new ground of rejection.***

McClelland et al discloses at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). Therefore, the encoded human

apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299. Additionally, the DNA sequence encoding human apolipoprotein 3 or its fragment may further include a leader sequence or portion thereof, a secretory signal or portion thereof of the apolipoprotein E gene (page 5, first paragraph). McClelland et al teaches specifically that **a clone having a perfect match with the expected sequence encoding human apoliporotein E3 with the Genbank accession #K00396 was used** (page 11, last sentence of first paragraph). The sequence encoding human apoliporotein E3 with the Genbank accession #K00396 is the same sequence reported by Breslow et al that has 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal sequence) of the present invention as evidenced by the teachings of Breslow et al. (see at least Fig. 3 and the attached sequence search). It is also noted that McClelland et al also teach the use of other human apoliporotein E isoforms or allelic variants (page 4, fourth and fifth paragraphs). McClelland et al further teaches that hypercholesterolemia is often associated with cardiovascular disease such as atherosclerosis (page 9, second paragraph), and that the method can be used to treat apolipoprotein-deficient animals, including apoE-deficient animals (page 9, last paragraph). McClelland et al also discloses that the reduction of plasma cholesterol concentrations and changes in the plasma lipoprotein distribution was presumably a result of the association of the human apoE protein with both apoB48- and apoB100-remnant lipoprotein particles, thereby increasing removal from the circulation (page 22, last sentence). Please noted that the DNA sequence encoding a fragment of human

apolipoprotein E3 that is truncated at the C-terminal taught by McClelland et al also encodes amino acids 1-203 and/or 1-220 of SEQ ID NO:2.

Accordingly, the method taught by McClelland et al has the same method steps and the same starting materials as the instant broadly claimed methods. Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 83 and 91-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over McClelland et al (WO 96/14837) as evidenced by Wetterau et al (J. Biol. Chem. 263:6240-6248, 1988), Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited

previously) and in view of French et al. (US 6,290,949). ***This is a new ground of rejection.***

McClelland et al discloses at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299. Additionally, the DNA sequence encoding human apolipoprotein 3 or its fragment may further include a leader sequence or portion thereof, a secretory signal or portion thereof of the apolipoprotein E gene (page 5, first paragraph). McClelland et al teaches specifically that **a clone having a perfect match with the expected sequence encoding human apoliporotein E3 with the Genbank accession #K00396 was used** (page 11, last sentence of first paragraph). The sequence encoding human apoliporotein E3 with the Genbank accession #K00396 is the same sequence reported by Breslow et al that has 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal sequence) of the present invention as evidenced by the

teachings of Breslow et al. (see at least Fig. 3 and the attached sequence search). It is also noted that McClelland et al also teach the use of other human apoliporotein E isoforms or allelic variants (page 4, fourth and fifth paragraphs). McClelland et al further teaches that hypercholesterolemia is often associated with cardiovascular disease such as atherosclerosis (page 9, second paragraph), and that the method can be used to treat apolipoprotein-deficient animals, including apoE-deficient animals (page 9, last paragraph). McClelland et al also discloses that the reduction of plasma cholesterol concentrations and changes in the plasma lipoprotein distribution was presumably a result of the association of the human apoE protein with both apoB48- and apoB100-remnant lipoprotein particles, thereby increasing removal from the circulation (page 22, last sentence).

McClelland et al does not teach specifically to administer the vector to an artery at the site of a lesion.

However, at the effective filing date of the present application, French et al already taught at least of direct intra-arterial injection or infusion of a recombinant replication defective adenoviral vector carrying gene sequences that are capable of ameliorating symptoms of cardiovascular diseases such as atherosclerosis or dyslipidemia or restenosis in a mammal (see at least Summary of the Invention, particularly col. 5; and examples 6-7).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of McClelland et al by also delivering the replication-defective adenoviral

vector to an artery at the site of a lesion in a mammal suffering a cardiovascular disease such as atherosclerosis in light of the teachings of French et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the specific localized gene delivery for ameliorating symptoms of cardiovascular diseases such as atherosclerosis or dyslipidemia or restenosis in a mammal using a recombinant replication defective adenoviral vector has been taught and successfully demonstrated by French et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of McClelland et al as evidenced by Wetterau et al, Breslow et al and in view of French et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 79, 83-91 and 94-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strittmatter et al (US 5,811,243) in view of Kahn et al. (US 6,756,523) and Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited previously) and in view of ***This is a new ground of rejection.***

Strittmatter et al disclosed at least a method comprising intravenous administering to a subject, including a human, combating Alzheimer's disease any suitable viral vector which carries a nucleic acid encoding ApoE (including ApoE1-ApoE4) or ApoE fragments (e.g., ApoE3 fragments 1-191, 1-244, 1-266 and 1-272)

(see at least Summary of the Invention; col. 3, lines 52-64; col. 4, lines 33-50; col. 5, lines 30-60; col. 6, lines 49-62). It is noted that lowering cholesterol level is desirable in any mammal, particularly for an adult human, and even more for a human patient at age about 80 years old and combating Alzheimer's disease. Therefore, the treated subject by the method taught by Strittmatter et al would fall within the broad scope of a mammal in need of lowering cholesterol and also at risk for developing atherosclerosis.

Strittmatter et al does not teach specifically the use of a replication-defective adenoviral vector or ApoE3 having SEQ ID NO:2, even though the reference discloses that any suitable viral vector and any ApoE, including ApoE3 and its fragments can be used.

However, at the effective filing date of the present application, Kahn et al already taught the use of a recombinant replication defective adenovirus vector for the expression of selected nucleotides in the cells of the central nervous system (see at least col. 3, lines 1-54).

Additionally, Breslow et al already cloned a human apolipoprotein E3 cDNA having 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal sequence) of the present invention (see at least Fig. 3 and the attached sequence search).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Strittmatter et al by also using a replication defective adenoviral vector containing a DNA sequence encoding ApoE fragments (e.g., ApoE3 fragments 1-191, 1-244, 1-266 and 1-272), including a DNA sequence encoding human ApoE3 fragments

obtained from the human cDNA clone taught by Breslow et al. in light of the teachings of Kahn et al. and Breslow et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Kahn et al already taught various advantages for using a recombinant replication defective adenovirus such as its great efficacy of infection, long term expression, wide host range and low toxicity (col. 3, lines 1-11). Additionally, the human ApoE3 cDNA was already available and cloned in the prior art since 1982. The modified method resulting from the combined teachings of Strittmatter et al., Kahn et al. and Breslow et al. is indistinguishable from the methods as broadly claimed because it has the same method steps and starting materials.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Strittmatter et al., Kahn et al. and Breslow et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D.
PRIMARY EXAMINER

```
            PF   28-APR-2000 JP 2000128919
            PR
            PI   SHINOBU FUJITA,HIROKI HAMANAKA,YUKO FUKUI,MINESUKE YOKOYAMA PC
              A01K67/027,A61K45/00,A61P25/28,A61P43/00,C12N5/10, PC
            C12N15/09//C07K14/775,
            PC   (C12N5/10,C12R1:91),C12N5/00,C12N15/00,(C12N5/00,C12R1:91) CC

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            FT   CDS             (61). .(1011).
FEATURES             Location/Qualifiers
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BASE COUNT      208 a    368 c    432 g    148 t
ORIGIN

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Percent Similarity:       100.00%        Conservative:    0
Best Local Similarity:    100.00%        Mismatches:      0
Query Match:              100.00%        Indels:          0
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US-09-827-854-15_COPY_1_203 (1-203) x BD004278 (1-1156)

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Qy      21 GluGlnAlaValGluThrGluProGluProGluLeuArgGlnGlnThrGluTrpGlnSer 40
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Qy      41 GlyGlnArgTrpGluLeuAlaLeuGlyArgPheTrpAspTyrLeuArgTrpValGlnThr 60
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Qy      81 LeuMetAspGluThrMetLysGluLeuLysAlaTyrLysSerGluLeuGluGluGlnLeu 100
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Qy     201 ProLeuVal 203
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Db     661 CCCCTGGTG 669

RESULT 5
HUMAPOE3
LOCUS       HUMAPOE3                1156 bp    mRNA    linear   PRI 24-NOV-2000
DEFINITION  Homo sapiens preapolipoprotein E (APOE) mRNA, complete cds.
ACCESSION   K00396
VERSION     K00396.1  GI:178850
KEYWORDS    apolipoprotein; apolipoprotein E; lipoprotein; polymorphism; very
            low density lipoprotein.
SOURCE      Homo sapiens.
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 355 to 1156)
  AUTHORS   Breslow,J.L., McPherson,J., Nussbaum,A.L., Williams,H.W.,
            Lofquist-Kahl,F., Karathanasis,S.K. and Zannis,V.I.
  TITLE     Identification and DNA sequence of a human apolipoprotein E cDNA
            clone
  JOURNAL   J. Biol. Chem. 257 (24), 14639-14641 (1982)
  MEDLINE   83082756
   PUBMED   6897404
REFERENCE   2  (bases 250 to 777)
  AUTHORS   Wallis,S.C., Rogne,S., Gill,L., Markham,A., Edge,M., Woods,D.,
            Williamson,R. and Humphries,S.
  TITLE     The isolation of cDNA clones for human apolipoprotein E and the
            detection of apoE RNA in hepatic and extra-hepatic tissues
  JOURNAL   EMBO J. 2 (12), 2369-2373 (1983)
  MEDLINE   84131952
   PUBMED   6199196
REFERENCE   3  (bases 1 to 1156)
  AUTHORS   Zannis,V.I., McPherson,J., Goldberger,G., Karathanasis,S.K. and
            Breslow,J.L.
  TITLE     Synthesis, intracellular processing, and signal peptide of human
            apolipoprotein E
  JOURNAL   J. Biol. Chem. 259 (9), 5495-5499 (1984)
  MEDLINE   84185684
   PUBMED   6325438
REFERENCE   4  (bases 88 to 1156)
  AUTHORS   McLean,J.W., Elshourbagy,N.A., Chang,D.J., Mahley,R.W. and
            Taylor,J.M.
  TITLE     Human apolipoprotein E mRNA. cDNA cloning and nucleotide sequencing
            of a new variant
  JOURNAL   J. Biol. Chem. 259 (10), 6498-6504 (1984)
  MEDLINE   84212473
   PUBMED   6327682
REFERENCE   5  (bases 577 to 624)
  AUTHORS   Gill,L.L., Peoples,O.P., Pearston,D.H., Robertson,F.W.,
            Humphries,S.E., Cumming,A.M. and Hardman,N.
  TITLE     Isolation and characterisation of a variant allele of the gene for
            human apolipoprotein E
  JOURNAL   Biochem. Biophys. Res. Commun. 130 (3), 1261-1266 (1985)
  MEDLINE   85279526
   PUBMED   2992507
REFERENCE   6  (sites)
  AUTHORS   Rall,S.C. Jr., Newhouse,Y.M., Clarke,H.R., Weisgraber,K.H.,
            McCarthy,B.J., Mahley,R.W. and Bersot,T.P.
  TITLE     Type III hyperlipoproteinemia associated with apolipoprotein E
            phenotype E3/3. Structure and genetics of an apolipoprotein E3
            variant
  JOURNAL   J. Clin. Invest. 83 (4), 1095-1101 (1989)
  MEDLINE   89198059
   PUBMED   2539388
COMMENT     [1]  corrected in [J. Biol. Chem. 258, 11422-11422 (1983)]. [J.
            Biol. Chem. 258, 11422-11422 (1983)]  correction of [1]. [4]
            epsilon-3 and variant.
            [5]  epsilon-2 allele.
            [6]  sites; mutations resulting in type III hyperlipoproteinemia.
            Apo E is a component of normal human very low density lipoprotein.
            There are six human apo E phenotypes known to result from a single
            structural gene, three of the common alleles being epsilon-4,
            epsilon-3 and epsilon-2. This sequence appears to be of the
            epsilon-3 allele. [1] argues that the apo E polymorphism involves
            mutations in the structural coding region; for example the
            epsilon-2 phenotype which is characterized by hyperlipoproteinemia
            is thought to result from a c to t change (arg to cys) at base 586
            below [3],[5]. The sequence shown is 57% homologous with human apo
            A-I and 81% homologous with rat apo E. For the epsilon-4 sequence,
```

see the separate entry.
[J. Biol. Chem. 258, 11422-11422 (1983)] is too extensively revised relative to [1] to record the
revisions in the FEATURES table. The sequence below is that of [J. Biol. Chem. 258, 11422-11422 (1983)]
and [3].
Apo E is located on chromosome 19 --Jackson, Bruns and Breslow , PNAS USA 81, 2945-2949 (1984) -- and is believed to be linked to the Apo C-II gene (see separate entry).
The two mutations causing type III hyperlipoproteinemia (apolipoprotein E phenotype E3/3) produces substitutions of Arg for Cys at amino acid 112 and Cys for Arg at amino acid position 142.
Draft entry and printed copy of sequence for [1] kindly provided by L.L. Gill, University of Aberdeen.
Complete source information:
Human liver [1],[J. Biol. Chem. 258, 11422-11422 (1983)],[2],[3], [4] and blood [5], cDNA to mRNA.

FEATURES Location/Qualifiers

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CDS 61. .1014
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mat_peptide 115. .1011
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variation 409
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variation 448
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variation 538
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variation 586
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/note="in epsilon-2 allele"
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variation 702
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variation 783
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/citation=[4]
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variation 858
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BASE COUNT 208 a 368 c 432 g 148 t
ORIGIN

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Percent Similarity:	100.00%	Conservative:	0
Best Local Similarity:	100.00%	Mismatches:	0
Query Match:	100.00%	Indels:	0
DB:	9	Gaps:	0

US-09-827-854-15_COPY_1_203 (1-203) x HUMAPOE3 (1-1156)

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Qy     21 GluGlnAlaValGluThrGluProGluProGluLeuArgGlnGlnThrGluTrpGlnSer 40
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy     81 LeuMetAspGluThrMetLysGluLeuLysAlaTyrLysSerGluLeuGluGluGlnLeu 100
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